

Antithrombotic drug use, cerebral microbleeds and intracerebral haemorrhage: a systematic review of published and unpublished studies

Pre-stroke antithrombotic drug use and microbleeds

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Title: 98 characters

Running title: 45 characters

Abstract: 253 words

Text: 3998 words

Figures: 3

Tables: 3

Funding:

The Stroke Prevention Research Unit in Oxford was funded by the UK Medical Research Council, the Dunhill Medical Trust, the Stroke Association, the BUPA Foundation, the National Institute for Health Research (NIHR), the Thames Valley Primary Care Research Partnership, and the NIHR Oxford Biomedical Research Centre. The Edinburgh Stroke Study was funded by a Wellcome Trust Clinician Scientist Award to Cathie Sudlow, and a Binks Trust research fellowship to Caroline Jackson. The Seoul National University Hospital study was supported by a grant from the Korean Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A080503).

Acknowledgements: In the Edinburgh Stroke Study, database and programming support were provided by Aidan Hutchison and Mike McDowall, and most of the scans were performed in the SFC Brain Imaging Research Centre Division of Clinical Neurosciences, University of Edinburgh, a core area of the Wellcome Trust Clinical Research Facility and part of the SINAPSE (Scottish Imaging Network – A Platform for Scientific Excellence) collaboration (www.sinapse.ac.uk) funded by the Scottish Funding Council and the Chief Scientist Office.. In the PITCH study, Dr Hilde Hénou, managed the radiological data.

Conflicts of interest: nil

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Key words: microbleeds, intracerebral hemorrhage, stroke, warfarin, antiplatelet agents

Abstract

BACKGROUND:

Cerebral microbleeds (MBs) are potential risk factors for intracerebral haemorrhage (ICH) but it is unclear if they are a contraindication for antithrombotic drugs. Insights could be gained by pooling data on MB frequency stratified by antithrombotic-use in cohorts with ICH and ischaemic stroke (IS)/TIA.

METHODS

We performed a systematic review of published and unpublished data from cohorts with stroke or TIA to compare the presence of MBs in:

1. Antithrombotic-users versus non-antithrombotic users with ICH
2. Antithrombotic-users versus non-users with IS/TIA
3. ICH versus ischaemic events stratified by antithrombotic-use

We also analysed published and unpublished follow-up data to determine the risk of ICH in antithrombotic-users with MBs.

RESULTS

In a pooled analysis of 1461 ICH and 3817 IS/TIA, MBs were more frequent in ICH versus IS/TIA in all treatment-groups, but the excess increased from 2.8 (2.3-3.5) in non-antithrombotic users to 5.7 (3.4-9.7) in antiplatelet-users and 8.0 (3.5-17.8) in warfarin-users (p-difference=0.01). There was also an excess of MBs in warfarin-users versus non-users with ICH (OR=2.7, 95%CI 1.6-4.4, p<0.001), but none in warfarin-users with IS/TIA (1.3, 0.9-1.7, p=0.33); p-difference=0.01. There was a smaller excess of MBs in antiplatelet-users versus non-users with ICH (1.7, 1.3-2.3, p<0.001), but findings were similar for antiplatelet-users with IS/TIA (1.4, 1.2-1.7, p<0.001); p-difference=0.25. In pooled follow-up data for 768 antithrombotic-users, presence of MBs at baseline was associated with a substantially increased risk of subsequent ICH (OR=12.1, 3.4-42.5, p<0.001).

CONCLUSIONS

The excess of MBs in warfarin-users with ICH compared to other groups suggests that MBs increase the risk of warfarin-associated ICH. Limited prospective data corroborate these findings but larger prospective studies are urgently required.

Introduction

Increasing use of gradient-recalled echo (GRE) MRI has highlighted the association between cerebral microbleeds (MBs) and ischaemic stroke (IS) and TIA.¹⁻⁶ MBs appear as small hypointense lesions on GRE-imaging,⁷ and correspond histologically to haemosiderin deposition in the perivascular space in association with severe microangiopathy.⁸ MBs appear to predict future intracerebral haemorrhage (ICH) in prospective observational studies of patients with either ICH^{9,10} or IS.^{2,11} This has led to concerns over the safety of antithrombotic drug use in patients with MBs, and some clinicians already regard MBs as a relative contraindication to warfarin-use.¹² However there is no clear evidence that MBs further increase the risk of antithrombotic-associated ICH. The number of outcomes in existing prospective studies has been small, and there has been insufficient power to stratify analyses by different drug treatments. Therefore there is a risk that clinicians are avoiding therapies of proven benefit unnecessarily.

In the absence of large prospective studies, case-case comparisons of MB frequency between antithrombotic-users and non-users stratified by stroke type might provide useful insights. If MBs do increase the risk of antithrombotic-associated ICH, then we should find an increased frequency of MBs in cases with antithrombotic-associated ICH compared to “spontaneous” ICH. In case these comparisons are confounded by clinical differences between antithrombotic-users and non-users, comparisons of MB frequency in ICH versus ischaemic events within treatment groups are also needed, and these should show relatively more cases with MBs in association with ICH versus IS/TIA among antithrombotic-users compared to non-users. We therefore aimed to study associations between antithrombotic-use and MBs by pooled case-case comparisons using data from both published and unpublished cohort studies with ICH and IS/TIA. We also looked at the

predictive power of MBs on baseline imaging after IS/TIA for risk of subsequent ICH in published and unpublished prospective studies.

Methods

We conducted a Medline search on 31st September 2009 using the terms “microbleed”, “microh(a)emorrhage”, “h(a)emorrhagic lacune”, and “stroke” or “TIA”, to identify cohort studies of patients with stroke and TIA who had undergone GRE-MRI to detect MBs. Further studies were identified by hand-searching the bibliographies of retrieved papers and reviews. We included studies of patients who had presented with an acute stroke or TIA, and that identified MBs in ≥ 10 subjects, and presented data on pre-morbid antithrombotic drug use according to the presence or absence of MBs, separating cases with IS/TIA and ICH, or these data were provided on application to the authors. We excluded studies of patients with vascular dementia, “chronic cerebrovascular disease,” or Binswanger’s disease. For each study we recorded inclusion and exclusion criteria, details of the imaging protocol, demographic data, prevalence of pre-morbid antithrombotic drug use, prevalence of previous stroke, and the proportion of patients with MBs. Where several papers had been produced from the same group, these were carefully reviewed to ensure that cohorts did not overlap. When it was not possible to determine this, data from the largest available cohort were taken.

We also obtained previously unpublished data from 6 cohorts with recent stroke or TIA – the Oxford Regional Neurosciences Centres Cohort, the Prognosis of Intracerebral Cerebral Haemorrhage (PITCH) study, the Institute of Neurology Cohort, the Edinburgh Stroke Study, the Nishiogi-chuo Hospital Cohort, and the Suiseikai Kajikawa Hospital Cohort. Details of the methods of these studies including the imaging protocols are shown in table 1. Those cohorts that included patients with ICH excluded haemorrhages secondary to tumour, trauma, aneurysmal bleeds, cavernous malformation and vasculitis. Patients in each cohort were assessed by a neurologist, and demographic and clinical data including pre-morbid medication were recorded. Scans were reviewed by at least two observers

who were either neurologists or neuroradiologists and experienced in examining GRE-MRI. MBs were defined as hypointense lesions on GRE T2*-weighted MRI images measuring <10mm, with the exception of the Nishiogi-chuo Hospital Cohort, in which MBs measured 2-5mm. All images were assessed blind to clinical data.

Finally we examined available prospective data on the risk of subsequent ICH in patients treated with antithrombotic medications who had undergone GRE-MRI following an index stroke or TIA. Prospective data were identified from the literature search and were available for 248 patients in the Oxford Neurosciences Centre Cohort who were also enrolled in the Oxford Vascular (OXVASC) study.¹³ OXVASC is a prospective population-based study of all vascular events, in which all patients are followed up at regular intervals after their index event. In addition all recurrent events in the population are identified through multiple overlapping methods of ascertainment.

Statistical Analysis

Using cross-sectional data from the above unpublished cohorts and all available published data from other cohort studies we calculated unadjusted odds ratios (OR) for finding MBs in:

1. Antithrombotic-users versus non-users with ICH
2. Antithrombotic-users versus non-users with ischaemic events
3. ICH versus IS/TIA stratified by antithrombotic-use

Using available prospective data we also calculated the OR for having a subsequent antithrombotic-associated ICH in patients with MBs versus patients without MBs.

If there were no patients with MBs in one of the above subgroups for any cohort study, we added 0.05 to all 4 cells in the 2x2 table to enable graphic representation and CI estimation.¹⁴ ORs were then combined using the Mantel-Haenszel method. Heterogeneity between individual studies and between subgroups of studies was determined using the Chi-squared test. In-house software was used

for this meta-analysis. If a patient was taking a combination of antiplatelet agents and warfarin, they were included in the group on anticoagulation and not in the group on antiplatelet agents.

Results:

Results from the previously unpublished cohorts, including numbers of patients with ICH and ischaemic events, numbers of patients with MBs stratified by stroke type, and baseline demographic and risk factor data are presented in table 2. The frequency of MBs ranged from 11-38% in cohorts with IS/TIA, and from 37-64% in cohorts with ICH. The frequency of premorbid antiplatelet and warfarin-use also varied between studies, ranging from 4-42% and 0-23% respectively.

The electronic search identified 174 articles. Of 70 potentially relevant cohort studies, 12 studies^{1, 5, 15-24} including six cohorts with ICH and eight cohorts with ischaemic cerebrovascular events met our inclusion criteria. Details of these studies are shown in table 3. Patients were recruited and scanned within 24 hours of stroke onset in three studies,^{1,5,6} and <90 days in a further seven studies.^{15-19,21,24} Three studies did not specify the delay between symptom onset and imaging.^{20,22,23} All studies used GRE-MRI to identify MBs, although magnet strength, imaging sequences, and slice thickness varied. The definition of MB size also varied: MBs measured $\leq 10\text{mm}$ in 4 studies,^{19,22-24} $\leq 7\text{mm}$ in 2 studies,^{1,15} $\leq 5\text{mm}$ in 6 studies,^{6,16-18,20,21} and size was not defined in one study.⁵

The pooled dataset included 1461 patients with ICH and 3817 patients with IS/TIA. Eight of the cohorts, contributing half the patients in this analysis were recruited from Asian populations, and the remaining studies were based in North American and European centres. The majority of data on patients with ICH came from Asian cohorts.

Results from the pooled analysis of published and unpublished data are shown in figure 1, stratified by event type. MBs were more frequent in warfarin-users with ICH compared to non antithrombotic-users (OR 2.7, 95% CI 1.6-4.4, $p<0.001$), but were not more frequent in warfarin-users with IS/TIA (OR=1.3, 0.9-1.7, $p=0.33$); p -value of the difference between pooled ORs=0.01. In comparisons involving antiplatelet-users, the relationship between MB frequency and antiplatelet-associated ICH was similar but weaker. MBs were more frequent in antiplatelet-users versus non antithrombotic-users with ICH (OR=1.7, 1.3-2.3, $p<0.001$), but the excess of MBs was not significantly different in the analysis of IS/TIA (OR=1.4, 1.2-1.7, $p<0.001$) - difference, $p=0.25$. Furthermore there was significant heterogeneity in the comparison involving antiplatelet-users with ICH, largely driven by a single out-lying cohort from Hiroshima. When data were re-analysed after removing this cohort, there was no longer a significant excess of MBs in antiplatelet-users versus non-users with ICH (OR=1.3, 0.9-1.8, $p=0.10$).

Where cohorts included both ICH and ischaemic events, the frequencies of MBs in ICH versus ischaemic events were compared stratified by treatment group (figure 2). MBs were more frequent in ICH versus IS/TIA among all treatment groups, but this difference was greater among warfarin-users (OR=8.0, 95% CI 3.5-17.8) and antiplatelet-users (OR=5.7, 3.4-9.7) compared to non antithrombotic-users (OR=2.8, 2.3-3.5); p -value of the difference between pooled ORs=0.01. However once again, there was significant heterogeneity in the comparison involving antiplatelet-users ($p=0.02$) largely driven by the cohort from Hiroshima, and when this was removed from the analysis the difference in MB frequency between antiplatelet-users with ICH and antiplatelet-users with ischaemic events fell (OR=2.6, 1.4-4.9), and was no different to the result seen in non antithrombotic-users; difference, $p=0.83$.

Prospective data were available for 241 patients (135 males, mean age 67 years) with IS/TIA in the Oxford Neurosciences Centre cohort; 203 patients (34 with MBs) were started or continued on antiplatelet agents, and 16 patients (2 with MBs) were started or continued on warfarin after their

index event. The follow-up period was censored at 30/09/2009, providing a mean(SD) follow-up of 27(13) months. In this time 2 patients who both had MBs on their baseline scan had an ICH on follow-up; one was an antiplatelet-user and the other a warfarin-user. Published prospective data were also available from 3 other cohorts,^{2,11,25} details of which are included in table 3. The pooled prospective data-set included 768 patients with stroke or TIA (90 ICH, 123 TIA, 555 IS), with a mean follow-up period of 27.7 months. Of these, 482 were prescribed antiplatelet agents after their index event and 164 were prescribed warfarin. Among all antithrombotic-users the odds of a subsequent ICH in patients with MBs versus patients without MBs was 12.1 (95%CI 3.4-32.5), $p<0.001$ (fig 3) and among warfarin-users it was 3.0 (0.5-17.5), $p=0.23$, although this latter analysis was limited by having only 5 cases of recurrent stroke due to ICH in warfarin-users.

Discussion:

This is the first systematic evidence of an association between warfarin-associated ICH and MBs. In a pooled analysis of 3817 patients with IS/TIA, and 1461 patients with ICH, we have shown an excess of MBs in warfarin-associated ICH, which was not found in warfarin-associated IS/TIA. Although there were relatively few data on warfarin-users, these preliminary results indicate that warfarin may be hazardous in patients with MBs. Similar but weaker associations between MB frequency and antiplatelet-associated ICH were also seen, but these results have to be interpreted with caution as there was significant heterogeneity between cohorts in analyses involving antiplatelet-associated ICH. The limited available prospective data also support the hypothesis that the presence of MBs increases the risk of future ICH as a complication of antithrombotic drug use. While we do not advise avoiding antithrombotic drugs in patients with MBs who have a high risk of future thromboembolic events, these data suggest that more prospective data on the safety of antithrombotic drugs in such patients are urgently required.

There are a number of caveats regarding our interpretation of the cross-sectional data. Firstly comparisons in this study are not adjusted for all potential confounders. For example warfarin-users are more likely to have a history of hypertension or past stroke than non-users,²⁶ and both risk factors are associated with an increased frequency of MBs.²⁷ However we did not find an excess of MBs in warfarin-users versus non-users with IS/TIA, although similar differences in risk factors might be expected between these groups. In comparisons of MB frequency in ICH versus IS/TIA within treatment groups, cases were probably better matched. In this analysis we expected to find an excess

of MBs in cases with ICH versus cases with IS/TIA in all treatment groups,^{4,16,21} but the relative frequency of MBs in warfarin-associated ICH was higher than the relative frequency in non antithrombotic-associated ICH. This again is consistent with the hypothesis that MBs are markers of increased bleeding risk on warfarin. Secondly, it is possible that warfarin causes MBs and this is the reason for the excess of MBs in warfarin-users with ICH. However if this were true, then we should have seen a similar excess of MBs in warfarin-users with IS/TIA as well.

Our results are more difficult to interpret for antiplatelet-users. There was a weak association between MBs and antiplatelet-use among patients with ICH in particular, which was similar in magnitude to that reported recently in a cohort of predominantly healthy elderly individuals.²⁸ However this association was largely driven by the results of one large Japanese cohort, and disappeared when the results of this cohort were excluded from the analysis. Heterogeneity between cohorts of antiplatelet-users was perhaps not entirely unexpected as there may be groups of antiplatelet-users at higher risk of future ICH. There is evidence that the risk of future ICH increases with the number of MBs identified on a baseline scan.^{9,10} Moreover, lobar MBs may be a marker for cerebral amyloid angiopathy, an increasingly recognized cause of antithrombotic-related ICH; and it is therefore possible that multiple lobar MBs increase the risk of antiplatelet-related ICH. We were unable to stratify our findings by the number of antiplatelet agents used or the number and location of MBs present, but we are continuing to collect data to carry out these subgroup analyses.

Prospective studies can provide more direct evidence about whether or not MBs increase the risk of antithrombotic-associated ICH, but so far have been limited by few warfarin-users, relatively short follow-up periods, and therefore insufficient numbers of outcome events to provide a reliable estimate of the risks of antithrombotic drug use in the presence of MBs.^{2,11,23,25} However, the limited prospective data that are available appear to show that MBs do increase the risk of ICH as a complication of antithrombotic-use. These results are also unadjusted for potential confounders, but are nevertheless consistent with the results of the pooled analysis of cross-sectional data, and

together make a compelling argument for the need for a collaborative prospective study of warfarin-users with microbleeds in particular.

Our review presents data on MB frequency in the largest number of antithrombotic users with stroke to date, but does have some limitations. As has already been mentioned, there are still few data on the prevalence of MBs in warfarin-users with ICH, and although MBs are more frequent in these cases compared to other subgroups, the confidence limits for these estimates are wide. Secondly more data are required on ICH in non-Asian cohorts. The risk of antithrombotic-associated ICH appears to be highest in Asian patients,²⁹ and so the apparent risk of antithrombotic-associated ICH in the presence of MBs may also differ between ethnic groups. Thirdly, our analysis might have underestimated the association between MBs and warfarin-associated ICH. Average haematoma volumes and case fatality rates are higher in warfarin-associated ICH compared to spontaneous ICH,²⁶ potentially reducing MB detection rates in this group because patients are too clinically unstable to be scanned, and because MBs might be obscured by larger haematomas associated with increased oedema and distortion of brain parenchyma. Furthermore our analysis is not limited to cases with incident ICH. Recurrent ICH is associated with a higher prevalence of MBs than incident ICH,³ and cases with recurrent ICH are less likely to be taking warfarin prior to their recurrent stroke.

In some of the Oxford cohort, the imaging technique was not always optimal for highlighting MBs. Hybrid imaging techniques incorporating gradient and spin echos such as TGSE have the advantage of being fast and therefore useful in busy one-stop neurovascular clinics, but are less sensitive than gradient echo imaging for detecting MBs.³⁰ Imaging sequences used by other studies in the systematic review also varied, and this might also have contributed to differences in the observed frequency of MBs.^{27,31} However, these issues are more relevant to inter-study comparisons, and should not have affected case-case comparisons between subgroups within each study.

ICH is the most feared complication of warfarin use, and is associated with very poor outcomes.²⁶ Warfarin-associated ICH makes up 14% of all ICH,³² and given the rising prevalence of atrial fibrillation and greater use of warfarin, its incidence is expected to rise.³³ Therefore any means of better identifying patients at risk of warfarin-related complications is vital. Our study provides further evidence that MBs are likely to indicate an increased risk of ICH associated with warfarin-use, and highlights the urgent need for more prospective studies of the safety of warfarin in patients with MBs. Data on the association between MBs and antiplatelet-associated ICH are less consistent, but addition of future observational studies to the meta-analyses published here might provide more reliable estimates.

Figures:

Fig 1. Proportions of antithrombotic users versus non-antithrombotic users with at least one microbleed stratified by type of medication in cases with (A) intracerebral haemorrhage, and (B) ischaemic stroke and TIA

Figure 2. Proportions of ICH events versus infarct/TIA events with visible MBs stratified by pre-morbid antithrombotic medication use.

Fig 3 Frequency of ICH on follow-up in antithrombotic-users with MBs versus antithrombotic-users with no MBs

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Table 1 Methods of previously unpublished cohort studies of patients with recent TIA and stroke

	Oxford Regional Neurosciences Centre	PITCH study, Lille University	Institute of Neurology	Edinburgh Stroke Study, Western General Hospital	Nishiogi-chuo Hospital	Suiseikai Kajikawa Hospital
Region	Oxford, UK	Lille, France	London, UK	Edinburgh, UK	Tokyo, Japan	Hiroshima, Japan
Study period	9/2000 - 12/2008	11/2004-	12/2000 - 2/2008	4/2002 - 4/2005	1/2003 - 9/2005	4/2006 - 3/2009#
Number	771	235	52	275	94	1396
Event	All stroke and TIA	ICH, Warfarin users with IS	ICH	All stroke and TIA	ICH	All stroke
Consecutive recruitment	No	Yes	Yes	No	Yes	Yes (from 10/2007)
Magnet Strength (T)	1.5	1.5	1.5	1.5	1.0	1.5
TR(ms)/TE(ms)	4000/95 & 530/14	800/22	300/40	620/15	675/15	800/26
Slice thickness (mm)	5	5	5	5	6	5
Gap thickness (mm)	1	1.5	1.5	1	1	1.5
Median delay (IQR) to scan (days)	20 (10-41)	6 (3-9)	27 (0-219)	22 (8-37)	All scanned ≤28 days	-

excludes 9/2007

Table 2 Numbers (%) with risk factors and on pre-morbid antithrombotic agents in previously unpublished cohorts with TIA and stroke

	Oxfordshire, UK		Lille, France	London, UK	Edinburgh, UK		Hiroshima, Japan		Tokyo, Japan
	Ischaemic stroke/TIA	ICH	ICH	ICH	Ischaemic stroke/TIA	ICH	Ischaemic stroke	ICH	ICH
	N=715 (348 TIA/ 367 stroke)	N=56	N=221	N=52	N=265 (10 TIA/ 255 stroke)	N=10	N=1064	N=332	N=94
Mean Age (SD) years	70 (12)	74 (10)	67 (13.6)	67 (10.5)	70 (\pm 13)	70 (\pm 7)	72 (12)	68 (13)	65 (11)
Males (%)	397 (56)	34 (61)	126 (57)	31 (60)	149 (56)	5 (50)	651 (61)	186 (56)	58 (62)
Number with MBs (%)	80 (11)	20 (36)	119 (54)	30 (58)	100 (38)	6 (60)	379 (36)	200 (60)	60 (64)
Risk factors									
Hypertension (%)	404 (57)	40 (71)	140 (63)	44 (85)	138 (52)	4 (40)	708 (67)	296 (89)	93 (99)
Diabetes (%)	93 (13)	8 (14)	34 (15)	6 (12)	22 (8)	1 (10)	290 (27)	73 (22)	10 (11)
Hyperlipidemia (%)	285 (40)	6 (11)	68 (31)	22 (43)	-	-	400 (38)	92 (28)	1 (1)
Previous stroke (%)	69 (10)	8 (14)	28 (13)	6 (12)	35 (13)	2 (20)	338 (32)	97 (29)	18 (19)
Previous TIA (%)	30 (4)	5 (9)	14 (6)	6 (12)	47 (18)	2 (20)	-	-	-
IHD (%)	118 (17)	7 (13)	30 (14)	9 (17)	62 (23)	3 (30)	-	-	3 (3)
AF (%)	51 (7)	13 (23)	21 (10)	7 (13)	55 (21)	0 (0)	-	-	2 (2)
Prior Antithrombotic use									
Warfarin (%)	25 (4)	9 (16)	25 (11)	2 (4)	10 (4)	0 (0)	118 (11)	56 (17)	2 (2)
Antiplatelet (%)	238 (33)	16 (29)	62 (28)	17 (33)	112 (42)	30 (30)	279 (26)	15 (5)	9 (10)

Table 3 Summary of published studies included in systematic review

Author, Reference	Region	Number and Stroke type	Mean age (yrs)	Male %	MB %	Antiplatelet Users %	Warfarin Users %	Previous Stroke %	MRI strength TR(ms)/TE(ms)	Mean(SD) Follow up (months)	Number with subsequent ICH
Imaizumi ¹⁵	Hokkaido Japan	202 ICH 135 LI	66 66	51 65	77 46	6 13	1 5	5 13	1.5 T 450/26	-	-
Lee ¹⁶⁻¹⁸	Seoul Korea	149 ICH 143 IS	62 65	50 52	68 35	22 12	16 none	25 28	1.5T 200 - 500/15	-	-
Nishikawa ²²	Osaka Japan	106 ICH	67	62	55	11	none	18	1.5T 889/23	-	-
Jeong ²⁰	Ilsan Korea	107 ICH	62	59	70	24	3	25	1.5T 284/20	-	-
Copenhaver ¹⁹	Washington USA	87 ICH	68	46	57	59	9	14	1.5T & 3.0T 800/20 875/11	-	-
Aleman ²¹	Uppsala Sweden	45 ICH 45 IS	67 67	53 53	64 18	27	7	19	1.5 T 500/14	-	-
Soo ²³	Hong Kong China	908 IS	68	58	28	27	3	20	1.5T 350/30	-	-
Schonewille ²⁴	Utrecht Netherlands	42 LI	NR	NR	21	43	12	31	1.5T 600/30-40	-	-
Boulanger ⁵	Calgary Canada	236 IS/TIA	NR	55	19	24	NR	41	3T 500/20	-	-
Ovbiagele ¹	Los Angeles USA	164 IS/TIA	71	48	35	52	6	18	1.5T 800/15	-	-
Nighogossian ⁶	Lyon France	100 IS	60	58	20	27	NR	26	1.5T 800/26	-	-
Prospective studies											
Orken ²⁵	Istanbul Turkey	141 IS	66	58	22	none	100	18	1.5T 640/15	46.5	2
Naka ¹¹	Hiroshima Japan	183 IS 83 ICH	67	63	35	66	none	NR	1T 4500/112	18.6	10
Fan ²	Hong Kong China	121 IS	68	68	36	80	6	41	1.5T 300/30	27.5	5

Abbreviations: IS=ischemic stroke, LI=Lacunar infarct, ICH=intracerebral haemorrhage, NR = not reported